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Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1654731> since 2018-10-31T09:17:26Z

Published version:

DOI:10.1002/mdc3.12360

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PURE AUTONOMIC FAILURE VERSUS PRODROMAL DYSAUTONOMIA IN PARKINSON'S DISEASE: INSIGHTS FROM THE BEDSIDE

Aristide Merola^{1,*}, Alberto J Espay², Maurizio Zibetti¹, Alberto Romagnolo¹, Michela Rosso¹,
Simona Maule³, Leonardo Lopiano¹

¹ Department of Neuroscience “Rita Levi Montalcini”, University of Turin, via Cherasco 15, 10124,
Torino, Italy

² Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of
Neurology, University of Cincinnati, Cincinnati, Ohio, USA

³ Department of Medical Sciences, Autonomic Unit and Hypertension Unit, University of Turin,
Corso Bramante 88, 10126 Torino, Italy

***Corresponding Author:** Aristide Merola MD, PhD

Department of Neuroscience “Rita Levi Montalcini”, University of Turin; Via Cherasco 15, 10124
Torino, Italy.

Tel & Fax: +39 0116335089.

e-mail: aristidemerola@hotmail.com

Word count: 788

Running title: dysautonomia as presenting symptom of PD

Keywords: Parkinson's disease; Pure Autonomic Failure; Dysautonomia

The authors report no financial disclosure, conflict of interest or funding source in relation to the
case reported in this manuscript

CASE REPORT

Autonomic failure, which may include orthostatic hypotension (OH), supine hypertension, bowel and bladder disturbances, impaired thermal regulation and sexual dysfunction, can be features of Parkinson's disease (PD) and other α -synucleinopathies. All patients with pure autonomic failure (PAF), most with multiple system atrophy (MSA) and 18% with PD will develop symptomatic OH [1]. However, the extent of central and peripheral norepinephrine deficiency, parasympathetic nuclei degeneration, and arterial baroreflex failure may be differentially impaired in these disorders [2, 3]. As a result, clinical features and prognosis of autonomic dysfunction in α -synucleinopathies may be more complex than previously envisioned.

A 68-year-old man was admitted to the emergency unit for syncope and chest pain associated with orthostatism. Over the prior 12 months he had reported three syncopal events, constipation, erectile dysfunction, and profuse sweating. Blood pressure (BP) was 148/98 mmHg, supine, and 80/50 mmHg, upright. Electrocardiography (ECG), 24h ECG monitoring, and coronary angiography were normal, while echocardiography revealed left ventricular hypertrophy. The autonomic evaluation showed nocturnal hypertension with a "reverse dipping" pattern on ambulatory BP monitoring; significant BP drop in the lying-to-standing test (53/28 mmHg at 3 minutes; normal < 20/10 mmHg [systolic/diastolic]); decreased heart rate variability (HRV) as measured by deep breathing test (Expiratory/Inspiratory ratio= 1.01; normal \geq 1.1), lying-to-standing test (30:15 ratio= 1.0; normal \geq 1.04), and Valsalva maneuver (Valsalva Ratio= 1.04; normal \geq 1.14); and markedly low catecholamine plasma levels in both supine and orthostatic positions (Figure 1). Brain magnetic resonance imaging, peripheral nerve conduction studies (bilateral evaluation of peroneal, tibial, ulnar, median, and sural nerves distal latencies, amplitudes, motor and/or sensory nerve conduction velocities), vestibular tests, carotid/vertebral Doppler ultrasonography and neurological examination were normal. A 123 I-Metaiodobenzilguanidine (123 MIBG) cardiac positron emission tomography

demonstrated widespread sympathetic denervation (Figure 1). He was managed with midodrine 15 mg/day, and fludrocortisone 0.1 mg/day. Three years later, he developed resting tremor in the right hand and foot, associated with mild bradykinesia. Brain [¹²³I] FP-CIT-SPECT (DAT-SCAN) showed abnormal radioligand binding affecting the left putamen. A diagnosis of PD was made and treatment with rasagiline (1 mg/day) started, lowering the Unified Parkinson's Disease Rating Scale (UPDRS) part III from 11/108 to 6/108. The Scale for Outcome in Parkinson's disease-Autonomic (SCOPA-AUT) and Non-Motor Symptom Scale (NMSS) scores were 30 and 50, respectively. Significant alterations were found in the cardiovascular, sexual function, gastrointestinal tract, and fatigue sub-items. Moreover, the patient reported excessive sweating, mild alterations of smell, and mild problems sustaining concentration. No alterations were reported in mood/cognition, perceptual problems/hallucinations, and urinary functions. Four years later, upon worsening of tremor and bradykinesia (UPDRS-III, 14/108); low-dose levodopa/carbidopa (50/12.5 t.i.d.) was administered for 2 weeks, followed by significant motor improvement (UPDRS-III, 7/108). However, OH worsened, with an increase of NMSS item 1 (lightheadedness when standing) frequency from 3 (frequent) to 4 (Very frequent). In addition, presyncopal episodes associated with standing were reported 1-3 hours after each levodopa dose, with documented BP falls > 30/15 mmHg (systolic/diastolic).

After more than 10 years from the onset of autonomic features, and 7 from motor features, dysautonomia with prominent OH remained a levodopa-limiting major source of disability with motor symptoms modestly improved with rasagiline 1 mg/day (UPDRS-III, 15/108).

In this letter we report the long-term follow-up of a patient with severe autonomic dysfunction as presenting symptom of PD. The clinical features initially suggested MSA or PAF, but the abnormal ¹²³MIBG scan and the low orthostatic catecholamine plasma levels argued against a diagnosis of MSA, and the profuse sweating was atypical for PAF (Table 1). The early differential diagnosis of α -synucleinopathies is challenging given the different prognosis (10-year survival rate of 33% in

MSA, 87% in PAF, 74% in PD+OH, and 93% in PD without OH [3]) and the heterogeneous pathogenic mechanisms involved (Table 1). MSA is characterized by glial cytoplasmic inclusions of α -synuclein, with central catecholaminergic deficiency, degeneration of parasympathetic nuclei and preserved peripheral sympathetic innervation [4]. Conversely, PAF and PD are characterized by neuronal inclusions of α -synuclein deposited as cytoplasmic Lewy bodies, differing only in their distribution. PAF affects predominantly peripheral structures [4], while PD additionally involve central structures (Table 1), as suggested by the frequent association between OH, cognitive impairment and REM sleep behavioral disorder [5].

The case reported in this letter highlights the clinical similarities between PD and PAF, raising the question of whether PAF represents a restricted Lewy body synucleinopathy or an early manifestation of PD, as proposed by Kaufmann and colleagues [6]. The possibility exists that certain biological processes, as yet unrecognized, may succeed in restricting Lewy body pathology to the peripheral autonomic nervous system (as lifelong PAF) or fail by allowing its slow spread into the central nervous system (as prodromal dysautonomia in PD). Understanding these biological processes may inform the development of future neuroprotective strategies in PD.

ACKNOWLEDGMENT

Authors acknowledge the contributions of the Neurology Unit staff of San Giovanni Battista Hospital, Turin.

AUTHORS' ROLES

- 1) Research project: A. Conception, B. Organization, C. Execution;
- 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
- 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

Aristide Merola: 1A, 1B, 1C, 3A

Alberto J Espay: 1B, 3A, 3B

Maurizio Zibetti: 1B, 1C, 3B

Alberto Romagnolo: 1B, 1C, 3B

Michela Rosso: 1B, 3B

Simona Maule: 1C, 3B

Leonardo Lopiano: 1B, 3B

ETHICAL STANDARD

The authors declare that they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

INFORMED CONSENT

The patient gave written informed consent to be anonymously described in this letter.

CONFLICT OF INTEREST AND FINANCIAL DISCLOSURES

Financial disclosure related to research covered in this article: the authors report no financial disclosure, conflict of interest or funding source in relation to the case reported in this manuscript

Full financial disclosure for the previous 12 months:

Dr. Merola has received grant support from UCB Pharma and speaker honoraria from CSL Behring, UCB Pharma and Teva Pharmaceuticals. He has received personal compensation from Edge Consulting S.r.l., MediK S.r.l. and Sthetos S.r.l.

Dr. Espay is supported by the NIH (1K23MH092735); has received grant support from CleveMed/Great Lakes Neurotechnologies, and the Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Abbvie, Chelsea Therapeutics, TEVA, Impax, Merz, Pfizer, Acadia, Cynapsus, Solstice Neurosciences, Lundbeck, and USWorldMeds; royalties from Lippincott Williams & Wilkins and Cambridge University Press; and honoraria from Abbvie, UCB, USWorldMeds, Lundbeck, Acadia, the American Academy of Neurology, and the Movement Disorders Society. He serves as Associate Editor of the Journal of Clinical Movement Disorders and on the editorial board of Parkinsonism and Related Disorders.

Dr. Zibetti received speaker and/or consulting honoraria from Medtronic, Lundbeck, UCB Pharma and Abbvie.

Dr. Romagnolo has received grant support from Abbvie and travel grants from Novartis and Merck Serono. He has received personal compensation from Edge Consulting S.r.l. and Sthetos S.r.l.

Prof. Lopiano received honoraria for lecturing and travel grants from Medtronic, UCB Pharma and AbbVie.

Dr. Rosso and Dr. Maule declare no conflicts of interests.

FUNDING STATEMENT

Nothing to declare.

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FIGURE CAPTIONS AND LEGENDS

Fig. 1

$^{123}\text{MIBG}$ SCAN, DAT-SCAN, AND PLASMA CATECHOLAMINE LEVELS

a) $^{123}\text{MIBG}$ scan demonstrated widespread cardiac sympathetic denervation; **b)** DAT-SCAN showed abnormal radioligand binding affecting the left putamen; **c)** catecholamine plasma concentrations showed low norepinephrine levels in both supine and standing positions